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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,957	02/03/2005	Jonathan S. Stamler	STAM3002 PCT	6780

23364 7590 12/15/2009

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ART UNIT	**PAPER NUMBER**
1612	
MAIL DATE	**DELIVERY MODE**
12/15/2009	PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JONATHAN S. STAMLER and ZHIQIANG CHEN

Appeal 2009-013530
Application 10/508,957
Technology Center 1600

Decided: December 15, 2009

Before DONALD E. ADAMS, ERIC GRIMES, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 75-84, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to a method of activating inactivated mitochondrial aldehyde dehydrogenase (mtALDH) in a patient who has received nitroglycerin therapy (claims 75-83) and a method for restoring clinical sensitivity to nitroglycerin to a patient who has lost sensitivity to nitroglycerin so that the patient no longer responds to nitroglycerin (claim 84). Claims 75 and 84 are illustrative:

75. A method of activating inactivated mtALDH in a patient who has received nitroglycerin therapy and has become nitroglycerin tolerant so the patient no longer responds to nitroglycerin comprising administering inactivated mtALDH activating effective amount of agent selected from the group consisting of dihydrolipoic acid, dithiothreitol and tris(2-carboxyethylphosphine).

84. A method for restoring clinical sensitivity to nitroglycerin to a patient who has lost sensitivity to nitroglycerin so that the patient no longer responds to nitroglycerin comprising administering to the patient a nitroglycerin sensitivity restoring amount of dihydrolipoic acid, dithiothreitol or tris(2-carboxyethylphosphine).

The Examiner relies on the following evidence:

Weischer et al. DE 4420102 A1 Dec. 14, 1995[1]

Kennedy et al., *Airway Response to Sublingual Nitroglycerin in Acute Asthma*, 246 JAMA 145-147 (1981).

Physcians' Desk Reference, "NITRO-BID® Plateau CAPS®" and "NITRO-BID® IV", 1220-1221 (43 ed. (1989)).

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[1] The Examiner relied upon the machine translation of this document found at http://www.worldlingo.com/wl/epo/epo.html? SEED=DE4420102 &SEED_FORMAT=E&..., accessed July 11, 2007 (Ans. 4).

Getz et al, *A Comparison between the Sulfhydryl Reductants Tris(2-carboxyethyl)phosphine and Dithiothreitol for Use in Protein Biochemistry*, 273 ANALYTICAL BIOCHEMISTRY 73-80 (1999).

Pruijn et al., *Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation*, 93 INTERSCIENCE 216-221 (1991).

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Appellants rely on the following evidence:

Horowitz et al., *Potentiation of the cardiovascular effects of nitroglycerin by N-acetylcysteine,* 68 CIRCULATION 1247-1253 (1983).

Joseph Loscalzo, *N-Acetylcysteine Potentiates Inhibition of Platelet Aggregation by Nitroglycerin*, 76 J. CLIN. INVERT 703-708 (1985).

Nishikawa et al., *Differential effects of N-acetylcysteine on nitroglycerin- and nicorandil-induced vasodila*, 32 J. CARDIOVASC. PHARMACOL. 21-28 (1998).

Tate et al., *Effects of N-acetylcysteine on nitroglycerin-induced relaxation and protein phosphorylation of porcine coronary arteries*, 13 HEART VESSELS 263-268 (1998).

The rejections presented by the Examiner follow[2]:

1. Claims 75-84 stand rejected under the written description provision of 35 U.S.C. § 112, first paragraph.

2. Claims 75-84 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

3. Claims 75-78, 81, and 84[3] stand rejected under 35 U.S.C. § 102(b) as being anticipated by Weischer.

4. Claims 75-77, 79, and 82 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Weischer and Pruijn.

5. Claims 75-83 stand rejected under 35 U.S.C § 103(a) as unpatentable over the combination of Weischer, Pruijn, and Getz.

We reverse.

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[2] The Examiner withdrew the rejection under 35 U.S.C. § 112, second paragraph (Ans. 3).

[3] The Answer contains a new ground of rejection (Ans. 3 ("Claim 84 is rejected under 35 U.S.C. § 102(b) as being anticipated by Weischer et al.")). According to the Examiner "[c]laim 84 had been inadvertently omitted during prosecution. This new ground of rejection corrects that oversight" (Ans. 13). The entirety of the Examiner's statement of the rejection of claim 84 is that "Weischer et al. teaches the use of alpha-lipoic acid, also known as dihydrolipoic acid, in combination with cardiovascular drugs, including specific embodiments for nitroglycerin (glyceryl trinitrate), for several conditions including angina and nitrate tolerance" (*id.*). This statement is included in the Examiner's statement of the rejection of claims 75-78 and 81. Accordingly, we consider the rejection of claim 84 together with claims 75-78 and 81.

New Matter:

ISSUE

Does Appellants' Specification provide written descriptive support for claims 75-84?

FINDINGS OF FACT

FF 1. Mitochondrial aldehyde dehydrogenase (mtALDH) "generates nitrite from nitroglycerin [glyceryl trinitrate, GTN (Spec. 1: 11)] and the nitrite is then converted to NO bioactivity. The enzyme becomes inactivated by GTN when GTN oxidizes the enzyme. When the enzyme becomes inactivated, the result is impaired sensitivity to nitrates which is GTN tolerance" (Spec. 9: 27-30).

FF 2. "Currently, nitrate tolerance is treated by increasing the dosage of nitrate administered, and this works for a while but not over the long term or for a chronic disorder" (Spec. 1: 23 - 2: 2).

FF 3. "Certain thiols reverse tolerance by reducing and thereby activating the oxidized mtALDH (or other component of the mtALDH system, e.g., a component regulating level of cofactor) and by facilitating removal of NO_2 groups from GTN" (Spec. 9: 30 - 10: 2).

FF 4. The Examiner finds that "[n]itrate tolerance is a loss of clinical sensitivity which is very broad and can be mild, moderate, severe, and many other degrees" (Ans. 5).

FF 5. The Examiner finds that the "[l]oss of clinical sensitivity is not . . . the same as complete tolerance in which a patient is not responsive at all" (*id.*).

FF 6. The Examiner finds that Appellants' Specification discloses the administration of dihydrolipoic acid, dithiothreitol, or tris(2-carboxyethylphosphine) to a patient that is nitroglycerin tolerant in a generic sense, e.g., a patient that has lost some degree of clinical sensitivity to nitroglycerin (Ans. 5).

FF 7. The Examiner finds that Appellants' Specification fails to disclose the treatment of a patient that is "completely" nitroglycerin tolerant (*id.*).

FF 8. The Examiner finds that Appellants' Specification fails to provide support for "the term 'nitroglycerin sensitivity restoring amount' of dihydrolipoic acid, dithiothreitol, or tris (2-carboxyethylphosphine)" as in claim 84 (*id.*).

PRINCIPLES OF LAW

"In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). A disclosure provides adequate written description if it conveys with reasonable clarity to those skilled in the art that the inventor was in possession of the invention. *See id.*

ANALYSIS

The inactivation of mtALDH results in nitroglycerin tolerance, which is defined as impaired sensitivity to nitrates (FF 1). We agree with the Examiner that the term "nitrate tolerance," as used in Appellants' Specification, reads on very mild to severe impairment of nitroglycerin sensitivity (FF 5). We also agree with the Examiner's finding that

Appellants' Specification discloses the administration of an mtALDH activating effective amount of an agent to a patient that has lost some degree of clinical sensitivity to nitroglycerin, e.g., a patient that is nitroglycerin tolerant (*see* FF 6).

We disagree, however, with the Examiner's findings regarding "complete tolerance" (*see* FF 5 and 7). Contrary to the Examiner's intimation, independent claims 75 and 84 do not require the patient to be completely tolerant to nitroglycerin (*Cf.* FF 5 and 7). Claims 75 and 84 simply require that "the patient no longer responds to nitroglycerin" at some dosage (Claims 75 and 84). According to the Specification, prior to Appellants' filing date the treatment for such a condition would have been to increase the dosage of nitroglycerin administered to the patient (FF 2). Appellants' Specification discloses an alternative to the known treatment of nitroglycerin tolerance. Specifically, Appellants disclose the administration of an mtALDH activating effective amount of an agent that reverses tolerance by activating the inactivated mtALDH enzyme (FF 3). The result of such a treatment is the restoration of nitroglycerin sensitivity, e.g., restoration of a patient's sensitivity to the administration of nitroglycerin at a particular dosage.

For the foregoing reasons we disagree with the Examiner's finding that Appellants' Specification fails to provide written descriptive support for claims 75-84.

CONCLUSION OF LAW

Appellants' Specification provides written descriptive support for claims 75-84. The rejection of claims 75-84 under the written description provision of 35 U.S.C. § 112, first paragraph, is reversed.

Enablement:

ISSUE

Have Appellants established error in the Examiner's prima facie case of lack of enablement?

FINDINGS OF FACT

FF 9. The Examiner finds that since there is a "high degree of unpredictability in the art for nitroglycerin, [and] it is unclear under what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug" (Ans. 8).

PRINCIPLES OF LAW

"In order to satisfy the enablement requirement of section 112, an applicant must describe the manner of making and using the invention 'in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same. . . . ' 35 U.S.C. § 112, para. 1." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1322 (Fed. Cir. 2005).

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993) (Examiner must provide a

reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

ANALYSIS

Appellants contend that "[t]he [claimed] invention is independent of the disease for which nitroglycerin is administered and is directed to restoring clinical sensitivity to nitroglycerin to a patient who has lost clinical sensitivity to nitroglycerin. . . . A condition that would not be treated by nitroglycerin is not encompassed by the claims" (App. Br. 8). We agree.

CONCLUSION OF LAW

Appellants have established error in the Examiner's prima facie case of lack of enablement.

The rejection of claims 75-84 under the enablement provision of 35 U.S.C. § 112, first paragraph, is reversed.

Anticipation:

ISSUE

Have Appellants established error in the Examiner's prima facie case of anticipation?

FINDINGS OF FACT

FF 10. Weischer teaches pharmaceutical combination preparations consisting of alpha-lipoic acid, dihydrolipoic acid and their oxidized or reduced R- or S-enantiomers as well as metabolites of alpha-lipoic acid and

at least an organic nitrate, calcium- antagonists or ACE-inhibitors (Weischer 1: 6-8; *see also* Ans. 9).

FF 11. Nitroglycerine is an example of an organic nitrate within the scope of Weischer's disclosure (Weischer 4: 10-12).

FF 12. Weischer teaches that it is known in the art that nitrates exhibit a "[s]lowdown of effectiveness . . . in spite of constant dosage during continuous therapy leading to so-called nitrate tolerance" (Weischer 5: 5-7).

FF 13. "The objective of [Weischer's] . . . invention is to make available combination preparations with synergetic effect for improved treatment of especially cardio-circulatory disorders" (Weischer 6: 14-17; *see* Ans. 9 (Weischer teaches the use of the disclosed composition for the treatment of "several conditions including angina and nitrate tolerance")).

FF 14. The Examiner finds that the patient population in Weischer "will inherently have some degree of tolerance as administration of nitroglycerin produces tolerance that increases over time and angina is a chronic condition" (Ans. 9).

PRINCIPLES OF LAW

On appeal to this Board, Appellants must show that the Examiner has not sustained the burden of showing that a claimed invention is unpatentable. *See Ex parte Yamaguchi*, 88 USPQ2d 1606, 1608 and 1614 (BPAI 2008) (precedential).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Thus, "[n]ewly discovered results of known

processes directed to the same purpose are not patentable because such results are inherent." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson,* 169 F.3d 743, 745 (Fed. Cir. 1999) (citations and internal quotation marks omitted).

Perricone v. Medicis Pharm. Corp., 432 F.3d 1368 (Fed. Cir. 2005) emphasizes this point by illustrating the difference between claims that recite a new use of an old composition and claims that recite a newly recognized benefit of an old method. *Perricone* involved two sets of claims, one directed to preventing sunburn damage and the other to treatment of skin sunburn. In each case, the claims required topical application of a fatty acid ester of ascorbic acid. The prior art described topical application of the same compound (among thirteen others) to skin, in an amount that encompassed the claimed effective amount. The *Perricone* court found that the claims directed to preventing sunburn damage to exposed skin surfaces were anticipated by the prior art, even though the prior art "[did] not disclose any benefit directed to skin sunburn, or any other specific skin disorders, as claimed" (*id.* at 1376). On the other hand, the court found that the claims directed to treating skin sunburn were directed to a new use of the prior art compounds, and therefore not anticipated, because the prior art "[did] not disclose topical application *to skin sunburn*" (*id.* at 1379). That is, the prior art did not disclose applying the compound to the same population (people with sunburn) as required by the claims. As the court explained, "[t]he issue is not . . . whether [the prior art] lotion *if applied* to skin sunburn would

inherently treat that damage, but whether [the prior art] discloses the application of its composition to skin sunburn" (*id.* at 1378).

ANALYSIS

The method of Appellants' claim 75 is drawn to the activation of inactivated mtALDH in a defined patient population. Specifically, Appellants' claim 75 requires the patient to be one who (1) has received nitroglycerin therapy and (2) has become nitroglycerin tolerant so the patient no longer responds to nitroglycerin (Claim 75). Claims 76-78 and 81 depend from claim 75.

The method of Appellants' claim 84 is drawn to the restoration of clinical sensitivity to nitroglycerin in a defined patient population. Specifically, Appellants' claim 84 requires the patient to be one who (1) has lost sensitivity to nitroglycerin and (2) no longer responds to nitroglycerin (Claim 84).

Appellants contend that Weischer does not teach the administration of a composition comprising dihydrolipoic acid to "a patient no longer responsive to nitroglycerin" (App. Br. 15). We agree. The Examiner failed to identify a teaching in Weischer of a patient population that meets the requirements of Appellants' claims. At best, the Examiner reasons that the patient population in Weischer "will inherently have some degree of tolerance as administration of nitroglycerin produces tolerance that increases over time and angina is a chronic condition" (FF 14). The Examiner directs attention to Weischer's "[p]age[s] 1-2 . . ., claims 1-3 and 21, and Page 4 - Table 1" to support this reasoning (Ans. 23). The cited sections of Weischer fail to teach a patient population that has received nitroglycerin therapy (as

required by claim 75), has lost sensitivity to nitroglycerin (as required by claim 84), or no longer responds to nitroglycerin (as required by claims 75 and 84). Accordingly, the Examiner has failed to establish that Weischer teaches a method wherein a composition within the scope of Appellants' claimed invention is administered to the same patient population required by Appellants' claimed invention.

CONCLUSION OF LAW

Appellants established error in the Examiner's prima facie case of anticipation. The rejection of claims 75-78, 81, and 84 under 35 U.S.C. § 102(b) as being anticipated by Weischer is reversed.

Obviousness:

PRINCIPLES OF LAW

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art." *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). On appeal to this Board, Appellants must show that the Examiner has not sustained the required burden. *See Ex parte Yamaguchi*, 88 USPQ2d 1606, 1608 and 1614 (BPAI 2008) (precedential); *Ex parte Fu*, 89 USPQ2d 1115, 1118 and 1123 (BPAI 2008) (precedential).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). It is proper to "take account of the inferences and creative steps that a person of ordinary skill in

the art would employ." *Id.* at 418. *See also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

The combination of Weischer and Pruijn:

ISSUE

Have Appellants established error in the Examiner's prima facie case of obviousness?

FINDINGS OF FACT

FF 15. The Examiner relies on Weischer as discussed above (Ans. 10).

FF 16. The Examiner finds that Weischer "does not expressly teach the use [of] dithiothreitol (DTT)" (*id.*).

FF 17. The Examiner finds that Pruijn teaches that "DTT and dihydrolipoic acid were able to reverse the inhibition of . . . alkylating agents" (*id.*).

ANALYSIS

Based on the foregoing evidence the Examiner concludes that "it would have been obvious to one of skill in the art at the time of the invention to substitute DTT for [the] dihydrolipoic acid" in Weischer's composition (Ans. 11).

Appellants contend that because Pruijn fails to teach or "suggest activating inactivated mtALDH, or even administering DTT to overcome nitroglycerine tolerance in a patient . . . P[ruijn] fails to remedy the deficiencies in W[eischer]" (Reply Br. 4-5). We agree.

CONCLUSION OF LAW

Appellants established error in the Examiner's prima facie case of obviousness.

The rejection of claims 75-77, 79, and 82 under 35 U.S.C § 103(a) as unpatentable over the combination of Weischer and Pruijn is reversed.

The combination of Weischer, Pruijn, and Getz:

ISSUE

Have Appellants established error in the Examiner's prima facie case of obviousness?

FINDINGS OF FACT

FF 18. The Examiner relies on the combination of Weischer and Pruijn as discussed above (Ans. 12).

FF 19. The Examiner finds that the combination of Weischer and Pruijn fails to teach the use of tris(2-carboxyethyl)phosphine (*id.*).

FF 20. The Examiner finds that Getz "teaches that the sulfydryl reductant tris(2-carboxyethyl)phosphine (TCEP) is an attractive alternative to commonly used dithiothreitol" (*id.*).

ANALYSIS

Based on the foregoing evidence the Examiner concludes that "[i]t would have been obvious to one of skill in the art at the time the claimed invention was made to substitute tris(2-carboxyethyl)phosphine for DTT, as suggested by Getz, and produce the instant invention" (Ans. 12).

Appellants contend that because Getz fails to teach or "suggest[] activating inactivated mtALDH, or overcoming nitroglycerin tolerance in a patient . . . G[etz] fails to remedy the deficiencies of [Weischer] . . . and P[ruijn]" (Reply Br. 5). We agree.

CONCLUSION OF LAW

Appellants established error in the Examiner's prima facie case of obviousness.

The rejection of claims 75-83 under 35 U.S.C § 103(a) as unpatentable over the combination of Weischer, Pruijn, and Getz is reversed.

REVERSED

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